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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/378,577	08/20/1999	WENYUAN SHI	60307-5001	9309

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EXAMINER
ZEMAN, ROBERT

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 02/11/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/378,577	SHI ET AL.	
	Examiner	Art Unit	
	Robert A Zeman	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 October 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *20* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10-4-2001 has been entered. Note that the after final amendment filed 7-26-2001 was not entered when submitted and Applicant's request for continued examination did not request entry. Since no amendment has been filed the rejections outlined in Paper No. 10 are still outstanding. Said rejections are reiterated in this Office action.

Information Disclosure Statement

The Information Disclosure Statement filed on 10-4-2001 is acknowledged. Cited references have been considered and a signed copy of said IDS is attached hereto.

Claim Rejections Maintained

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 5, 11 and 13-16 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the topical treatment using chimeric monoclonal antibodies, does not reasonably provide enablement for the treatment for the oral ingestion of tissue from transformed host is maintained for reasons of record.

Applicant argues that the state of the art in genetic manipulation of expression in plants is far more developed than is suggested by Examiner's comments. Specifically, Applicant cites two references (Thomzik, *Agrobacterium*-mediated Transformation of Stem Disks from Oilseed Rape (*Brassica napus* L.) and Topping et al., *Agrobacterium*-mediated Transformation of *Arabidopsis thaliana*) to "demonstrate the similarity of the techniques used to transform the respective plants and thereby express foreign proteins". Applicant further argues that the teachings of Thomzik demonstrate that the transformation of *Brassica* was known in the art at the time of the instant invention. Applicant further argues, "The absence of a specific disclosure of a method for expressing monoclonal antibodies in *Brassica* should not be viewed as a lack of enablement because those skilled in the art would be able to transform *Brassica* using the teachings of the specification". Applicant cites articles by Tacket et al. (Nature Medicine, Vol. 4, pages 607-609) and Kipriyanov et al. (Molecular Biology, Vol. 12, pages 173-201) to illustrate the state of the art. Tacket et al. is cited since they disclose the expression of viral antigens by transgenic potatoes, while Kipriyanov et al. is cited since the proclaim "plants are capable of synthesizing and assembling virtually every kind of antibody molecule, ranging from the smallest antigen-binding domains and fragments to full length and even multimeric antibodies". Applicant concludes by stating the aforementioned references indicate the state of the art is broader than asserted by Examiner and hence the rejection should be withdrawn.

Applicant's arguments have been fully considered and have been found to be non-persuasive. While Applicant is correct that in stating that Thomzik discloses the transformation of Oilseed Rape (*Brassica napus* L.) using *Agrobacterium*, the basis for his assertion that said methods are the same as those for transforming *Arabidopsis* is not understood. In fact, Thomzik teaches the opposite. On page 79, first paragraph, Thomzik states "Transformation protocols are relatively specific for cv. Westar and cannot be extended to most of the other spring and none of the winter varieties...". Since the disclosed protocols only are effective with certain varieties within the same species, it is extremely remote that said protocols would be effective in another species. With regard to the teachings of Tacket et al. and Kipriyanov et al., Tacket discloses the expression of viral antigens (not antibodies) in a species of plant unrelated to *Brassica*. Additionally, Kiprayanov's assertion cannot be construed to mean "all plants can express all antibodies". Consequently, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Applicant describes procedures for the use of *Arabidopsis thaliana* for the production of human/mouse chimeric monoclonal antibodies with specificity for *Streptococcus mutans*. Applicant fails to describe what procedures would be used when the plant species *Brassica*, or other edible plant, is used in lieu of *Arabidopsis*.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 3 and 9 under 35 U.S.C. 112, second paragraph, as being vague and indefinite through the use of the phrase "step of preparing" is maintained for reasons of

record. Applicant argues in Paper No. 7 that it is obvious that the "preparing step" refers to the chimeric antibodies of the antecedent claim. Applicant's arguments have been fully considered and have been found to be non-persuasive. As stated in the original rejection, it is unclear precisely what the "step of preparing" is referring to. It is suggested that "wherein the step of preparing further comprises..." be changed to "wherein step c) further comprises".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claims 1, 6 and 7 under 35 U.S.C. 102(b) as being anticipated by Lehner (U.S. Patent 5,352,446) is maintained for reasons of record. Lehner discloses the use of an orally administered murine monoclonal antibody (see column 3 lines 46-52 and column 4, lines 4-13) for the treatment and prevention of dental caries in man (see column 2, line 31-32). Lehner further discloses that said monoclonal antibody has specificity for *Streptococcus mutans* and can be administered in gum, mouthwashes, or lozenges. Additionally, Lehner discloses that monoclonal antibodies against *S. mutans* antigens passively immunize and provide inhibition of the development of *S. mutans* on teeth for extended periods of time when applied topically (see column 2, lines 16-21).

In response to Applicant's argument in Paper No. 7 that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., monoclonal antibodies are chimeric) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 1-4, 6-10, 12 and 17 under 35 U.S.C. 103(a) as being unpatentable over Ma et al. (European Journal of Immunology 1994 Vol. 24 (1) pages 131-138) in view of Adair et al (U.S. Patent 5,877,293) is maintained for reasons of record. As previously

stated in the previous office action, Ma et al. disclose methods for the production of chimeric monoclonal antibodies against *Staphylococcus mutans* in transgenic tobacco plants to be used in the treatment of dental caries in humans and other mammals (see page 131, second paragraph). The disclosed methods include: the cloning of heavy and light chain genes (see page 132); plant transformation and regeneration (see page 132); antibody chain detection (see pages 132-133); and measurement of chimeric antibodies and their binding capacities (see pages 133-134). Ma et al. differs from the claimed inventions in that both the heavy and light chains of the chimeric monoclonal antibodies are derived from murine antibodies. However, Adair et al. disclose methods for the production of chimeric antibodies where the light chains are derived from murine antibodies and the heavy chains are derived from human antibodies. Consequently, it would have been obvious to one of skill in the art at the time the invention was made to use the methods of Adair et al. to "humanize" the chimeric antibodies disclosed in the methods of Ma et al. in order to take advantage of the reduced antigenicity and the increased therapeutic effectiveness of "humanized" (chimeric) antibodies. This "humanizing" consists of replacing the murine heavy chain sequences of Ma et al. with the human heavy chain sequences of Adair et al. in the expression vectors of Ma et al. It should be noted that humanizing antibodies is a standard procedure used in most immunology laboratories. That, and coupled with the fact that Ma et al. suggests "incorporating other regions such as the complement binding region of human IgG" (see page 137, second paragraph) and Adair et al. state that chimeric monoclonal antibodies are less antigenic to humans and hence more effective therapeutically (see column 1 lines 52-65), one would have a high expectation of success in making the required antibodies and using them to treat or prevent dental caries.

Applicant argues that the antibodies disclosed by Ma et al. differ from those of the instant invention in that the antibodies of Ma et al. are entirely murine in origin. Applicant further argues the humanization of the antibodies, as disclosed by Adair et al, merely reduces the incidence of HAMA and does not engage the effector apparatus of the human immune response. Applicant further states that the combination of the cited references would not teach or suggest the instant invention. Applicant concludes by arguing the cited references do not teach or suggest the use of chimeric antibodies to bring the effector apparatus of the human immune system to bear on an infectious or otherwise pathological site in the body. Applicant's arguments have been fully considered and have been found to be non-persuasive. Applicant is reminded that the aforementioned rejection is based on the combination of the cited references (see above) and not independently. Said combination clearly encompasses all the limitations of the claimed invention. Additionally, as pointed out by Applicant, the construction of chimeric and humanized antibodies and the tailoring of the constant regions (i.e. selection of isotypes specific for cell mediated cytotoxicity) are well known in the art (see Kipriyanov et al., Molecular Biology, Vol. 12, pages 173-201).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A Zeman whose telephone number is (703) 308-7991. The examiner can normally be reached on M-Th 7:30 am - 5:00 pm and Alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Donna Wortman can be reached on (703) 308-1032. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

DONNA WORTMAN
PRIMARY EXAMINER

Robert A. Zeman
February 11, 2002